## REMARKS

### I. Status of Claims

Claims 17-22 and 24-30 are pending in the present application. Claims 26-28 and 30 have been allowed. Claims 17-19, 21-22, 24-25 are rejected and claim 20 is objected to. Claim 29 is withdrawn.

### II. Rejection under 35 U.S.C. § 103(a)

Claims 17-19, 21, 22 and 25 are rejected under §103(a) as allegedly being unpatentable over Costantino *et al.* (*Vaccine* 10:691-698, 1992) ("Costantino") in view of Seid Jr. *et al.* (US 7,118,757) ("Seid") and O'Hagan (J. Pharm. Pharmaco. 50: 1-10, January 1998) ("Hagan").

Applicants respectfully traverse the rejection and its supporting remarks.

1. *Seid et al.(Seid)*

The Examiner maintains that Seid teaches a vaccine formulation comprising OMVs. However, Seid does not provide evidence that OMVs were isolated or that OMVs were used in combination with MenC-$CRM_{197}$. Example 1B describes a protocol to isolate and purify OMVs, but it does not appear that any OMVs were ever actually produced. Furthermore, none of the data that is presented in the Seid disclosure includes OMVs or combinations of MenC-$CRM_{197}$ with OMVs. As was stated in the response to the final Office Action dated April 28, 2008, references to OMVs seem to be made as part of sweeping statements regarding what the invention may be. However, the claimed invention of the Seid disclosure makes no mention of OMVs (see claims 1-9 of US Patent No. 7,118,757).

The Examiner also states that Applicants' conclusions "that OMVs are strikingly absent in the combination of Seid's ('757) proteins with capsular components and that Seid *et al.* did not think of combining OMVs with capsular polysaccharides, are inaccurate." Applicants did not intend to imply that the words never appeared in the patent specification. Rather, applicants were

attempting to apply the same view that one of skill in the art would apply in reading the teachings of the '757 specification. One of skill in the art would first and foremost look to the work actually conducted just as if reading a published paper, which in the '757 specification appears to be expression of recombinant polypeptides derived from OMP tested with MenC-capsular polysaccharide. While the Examiner is likely correct that OMVs include OMP, it does not necessarily follow that OMVs can be combined predictably with MenC-capsular polysaccharides based solely upon an experiment using recombinant polypeptide from one protein that may be present in OMVs. One of skill in the art wouldn't merely accept the statements in the specification regarding OMVs as true without supporting data. Since the Examiner has not pointed to any working example actually disclosed in the '757 specification regarding the use of MenC-capsular polysaccharides in combination with OMVs, then one of skill would insist upon experimental evidence to demonstrate that this combination would work given that OMVs may behave quite differently than isolated polypeptides. OMVs are much more complicated as they include a number of different outer membrane proteins as well as the lipid bilayer. Therefore, there is no expectation of success unless the Examiner can demonstrate that one of skill in the art could predict the behavior of OMVs in a vaccine formulation based upon the behavior of isolated polypeptides and vice-versa.

Based on the reasons set forth above, the Examiner has not shown that one of skill in the art would have had a reasonable expectation of success in combining the vaccine formulation comprising MenC oligosaccharide conjugated to $CRM_{197}$ of the Costantino disclosure with MenB OMVs.

2. *O'Hagan (Hagan)*

The Examiner's assertion that "with regard to Applicants' alleged unpredictable results depicted in Table 3 of the instant invention…[it should be noted that] [t]he claims as presented currently do not require that the MF59 adjuvant in the claimed immunogenic composition selectively increase or decrease immune response to one or both of the antigenic components present therein," is confusing because the argument being made by the Applicants was not directed toward the claims, but to the fact that Table 3 is an example of experimental data showing the

unpredictable nature of the MF59 adjuvant when used in untested antigen combinations. Applicants respectfully request clarification – is the Examiner acknowledging that one of skill in the art would not know whether MF59 would increase the immune response?

The Examiner also points out that, "O'Hagan concluded that MF59 adjuvant is safe and effective in main in combination with a **variety** of antigens," [emphasis added]. Thus, the Examiner has not demonstrated that O'Hagan teaches that MF59 is effective in **all** antigens or combination of antigens. While this conclusion may be extended to include Group C meningococcal oligosaccharide-$CRM_{197}$, it does not extend to include the combination of MenC-$CRM_{197}$ and MenB OMV. Therefore, one of skill in the art would need to experimentally determine whether MF59 would be an effective adjuvant with a given antigen combination. To that end, the unpredictable results of Table 3 serve as an example of experimental data showing that MF59 is **not** predictably effective for **all** antigens or antigen combinations in generating an efficacious vaccine, or at the very least that additional optimization would need to be performed. Thus, the Examiner has not demonstrated that one of skill in the art could predict the efficacy of using MF59 in a vaccine conjugate comprising MenC-$CRM_{197}$ and MenB OMV absent performing an experiment. If this is not predictable without an experiment, one of skill in the art would have no reasonable expectation of success.

The Examiner further notes that:

> Applicants' argument that MF59 is not the only other adjuvant in existence, and that line 37 in column 12 through line 2 in column 13 of Seid ('513) identify at least six classes of adjuvants that include 17 different adjuvants, and that from this list alone, one of skill in the art would have seventeen adjuvants to test to see which if any may increase the antigenicity of the composition of Costantino *et al.* to better than that provided by the adjuvant already in the composition, is irrelevant.

The Supreme Court in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (US 1966) held that one of the four obviousness factual inquiries is to determine the scope and content of the prior art. Thus, given that adjuvants are not entirely predictable and that a reasonable expectation of

success in using MF59 with untested antigens or antigen combinations has not been establish, it becomes relevant to know all of the possible adjuvants that one of skill in the art would test in order to experimentally determine which adjuvants, if any, would work with a given antigen combination. The Examiner has selected the Hagan article because MF59 is used in the claims, but it is very likely that many of the adjuvants listed in Seid ('513) have similar review articles discussing, and even praising, the adjuvant being reviewed. It is in this context that an obviousness rejection in an unpredictable art must be reviewed. Thus, one of skill in the art would have known that at the time of the instant invention, the state of the art included very many adjuvants. As discussed above, the use of an adjuvant with an untested antigen combination is unpredictable. Therefore, one of skill in the art would need to test a variety of adjuvants to determine which, if any, will be effective with the given antigen combination. Even though the Seid ('513) "was not even applied as a part of this art rejection," it is a relevant prior art reference that discloses a variety of other adjuvants that would need to be tested. One of skill in the art would "look into" Seid ('513) for alternatives to MF59, because there is no reasonable expectation that MF59 would work better than alum with the MenC-$CRM_{197}$ and MenB OMV combination of the instant invention.

Thus, the Examiner has not shown that one of skill in the art would have had a reasonable expectation of success in using MF59 with the antigen combination of MenC-$CRM_{197}$ and MenB OMV.

3. *Combination of references*

Based on the reasons set forth above, the Examiner has not established a *prima facie* case of obviousness. While Costantino teaches a vaccine formulation comprising MenC oligosaccharide conjugated to $CRM_{197}$, it does not teach the use of MenB OMV and the MF59 adjuvant in the conjugate vaccine and therefore cannot provide a reasonable expectation for success of the combination. As stated above Seid does not sufficiently teach MenB OMVs to give a reasonable expectation of success for its use in the Costantino vaccine conjugate. Furthermore, Hagan gives no reasonable expectation of success for the use of MF59 in the specifically claimed use of the antigens MenC-$CRM_{197}$ and MenB OMV. MPEP § 2141.01 states that when applying 35 U.S.C. 103, the

tenet of reasonable expectation of success being the standard with which obviousness is determined, must be adhered to. Therefore, it is clear that one of skill in the art could not combine Costantino, Seid, and Hagan and have a reasonable expectation for success in producing the instant invention.

Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 17-19, 21, 22, and 25 under §103(a).

**III. Rejection under 35 U.S.C. § 103(a)**

Claim 24 is rejected under §103(a) as being allegedly unpatentable over Costantino *et al.* (*Vaccine* 10:691-698, 1992) ("Costantino") in view of Seid Jr. *et al.* (US 7,118,757) ("Seid") and O'Hagan (J. Pharm. Pharmaco. 50: 1-10, January 1998) ("Hagan") in further view of Seid J. *et al.* (US 6,638,513).

Applicants respectfully traverse the rejection and its supporting statements, provided, that applicants acknowledge that they were mistaken in their interpretation of dependent claim 24. Claim 24 claims "a carrier comprising polylactic acids or polyglycolic acids," as an alternative to $CRM_{197}$, since independent claim 17 only claims "a carrier." As such, the claimed invention in claim 24 is an immunogenic composition comprising MenC-capsular polysaccharide conjugated to polylactic acids or polyglycolic acids, MenB OMV, and MF59.

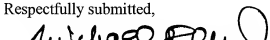
As discussed above, the Examiner has not established a *prima facie* case of obviousness as there is no reasonable expectation of success for the particular combination of Costantino, Seid ('757), and O'Hagan. The Examiner has not demonstrated how Seid '513 could provide a reasonable expectation of success where the other art cited has not. Applicants therefore respectfully request that the Examiner withdraw the rejection of claim 24 under §103(a).

## CONCLUSION

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 223002100100. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: January 23, 2009

Respectfully submitted,

By 

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